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Original article

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Racial/ethnic differences in the epidemiology of ovarian cancer: a pooled analysis of 12 case-control studies

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Abstract

Background: Ovarian cancer incidence differs substantially by race/ethnicity, but the reasons for this are not well understood. Data were pooled from the African American Cancer Epidemiology Study (AACES) and 11 case-control studies in the Ovarian Cancer Association Consortium (OCAC) to examine racial/ethnic differences in epidemiological characteristics with suspected involvement in epithelial ovarian cancer (EOC) aetiology.

Methods: We used multivariable logistic regression to estimate associations for 17 reproductive, hormonal and lifestyle characteristics and EOC risk by race/ethnicity among 10 924 women with invasive EOC (8918 Non-Hispanic Whites, 433 Hispanics, 911 Blacks, 662 Asian/Pacific Islanders) and 16 150 controls (13 619 Non-Hispanic Whites, 533 Hispanics, 1233 Blacks, 765 Asian/Pacific Islanders). Likelihood ratio tests were used to evaluate heterogeneity in the risk factor associations by race/ethnicity.

Results: We observed statistically significant racial/ethnic heterogeneity for hysterectomy and EOC risk ($P = 0.008$), where the largest odds ratio (OR) was observed in Black women [OR = 1.64, 95% confidence interval (CI) = 1.34–2.02] compared with other racial/ethnic groups. Although not statistically significant, the associations for parity, first-degree family history of ovarian or breast cancer, and endometriosis varied by race/ethnicity. Asian/Pacific Islanders had the greatest magnitude of association for parity ($\geq$3 births: OR = 0.38, 95% CI = 0.28–0.54), and Black women had the largest ORs for family history (OR = 1.77, 95% CI = 1.42–2.21) and endometriosis (OR = 2.42, 95% CI = 1.65–3.55).

Conclusions: Although racial/ethnic heterogeneity was observed for hysterectomy, our findings support the validity of EOC risk factors across all racial/ethnic groups, and further suggest that any racial/ethnic population with a higher prevalence of a modifiable risk factor should be targeted to disseminate information about prevention.

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Key Messages

- Considerable racial/ethnic differences exist in ovarian cancer incidence, yet the cause of these differences remains largely unknown.
- The objective of this study was to examine the association between 17 reproductive, hormonal and lifestyle factors and ovarian cancer risk by race/ethnicity (Non-Hispanic Whites, Hispanics, Blacks, Asian/Pacific Islanders) using data from the African American Cancer Epidemiology Study and the Ovarian Cancer Association Consortium.
- We observed heterogeneity by race/ethnicity in the association between hysterectomy and ovarian cancer risk ($P = 0.008$), where the greatest magnitude of the association was observed in Black women (OR = 1.64, 95% CI = 1.34–2.02) compared with other racial/ethnic groups.
- Our findings support the validity of ovarian cancer risk factors among all racial/ethnic groups, and highlight the need for a greater representation of minority racial/ethnic groups in epidemiological studies of ovarian cancer to elucidate the causes of racial/ethnic differences in ovarian cancer incidence.

Introduction

Ovarian cancer incidence differs appreciably by race/ethnicity.[1] Data from the Surveillance, Epidemiology, and End Results programme for 2010–14 indicate that in the USA, the age-adjusted ovarian cancer incidence rate is highest in White women (12.2 per 100 000) followed by Hispanics (10.6 per 100 000), Asian/Pacific Islanders (9.5 per 100 000), and Blacks (9.4 per 100 000).[2] The causes of the observed differences in incidence are likely multifactorial, yet remain relatively unknown because of the under-representation of non-White women in epidemiological studies of ovarian cancer.

There are considerable differences in the prevalence of risk factors for ovarian cancer by race/ethnicity, which may contribute to the inter-group variation in ovarian cancer incidence rates. For example, the National Center for Health Statistics reports that Hispanic and Black women have a greater number of pregnancies,[3] and National Health and Nutrition Examination Survey data suggest that the prevalence of obesity among adult women is higher for Black and Hispanic women at 58.6% and 40.7%, respectively.[4] To date, only four studies[5–8] have compared race- or ethnicity-specific associations in ovarian cancer. These studies mainly focused on White and Black women, yet each study had fewer than 150 Black women with ovarian cancer. Only one study reported risk factor associations among Hispanic women[5] and Asian/Pacific Islanders were not included in any of these studies. To address this knowledge gap, we capitalized on existing data from the Ovarian Cancer Association Consortium (OCAC)[9] and the largest case-control study of African American women with ovarian cancer, the African American Cancer Epidemiology Study (AACES),[10] to examine race/ethnicity-specific associations of various characteristics known or suspected to play a role in the aetiology of epithelial ovarian cancer (EOC).

Methods

Participating studies

We included AACES and any OCAC study that collected epidemiological risk factor data and had at least 10 cases that self-reported a racial/ethnic group other than Non-Hispanic White. Table 1 provides the characteristics of the 12 population-based case-control studies contributing to this analysis.

Epidemiologic variables

Individual-level epidemiological data from each study were pooled and harmonized for the following established or suggested EOC risk factors: parity (0, 1, 2, ≥3 live births); duration of oral contraceptive use (never use, <5 years, ≥5 years); first-degree family history of ovarian or breast cancer (yes, no); recent body mass index (BMI) (normal weight: <25 kg/m^2, overweight: 25–29.9 kg/m^2, obese: ≥30 kg/m^2); hysterectomy at least 1 year before the reference date (interview date for controls or diagnosis date for cases) (yes, no); tubal ligation at least 1 year before the reference date (yes, no); age at menarche (<12, 12–13, ≥14 years); history of endometriosis (yes, no); education (<high school, high school graduate/higher education); body powder exposure (never use, any regular genital use, only non-genital use); breastfeeding (yes, no); regular use of aspirin (yes, no), acetaminophen (yes, no), non-steroidal anti-inflammatory drugs (NSAIDs) (yes, no); hormone therapy (yes, no); estrogen-only hormone therapy (yes, no). The following variables were not available or set to missing for certain sites (acronyms: see Table 1): body powder exposure (CON, OVA, STA, UCI); endometriosis (OVA, STA); analgesic medications (OVA, STA); BMI (OVA, STA); tubal ligation (UCI); breastfeeding; (UCI) and estrogen-only hormone therapy use (AUS, CON, STA). For parity,

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Table 1. Characteristics of 12 case-control studies included in the analyses, $n = 27074$

				Race/ethnicity							
				Non-Hispanic White ($n = 22537$)		Hispanic ($n = 966$)		Black ($n = 2144$)		Asian/Pacific Islander ($n = 1427$)	
Case-control studies	Acronym	Location	Dates of interview	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
African American Cancer Epidemiology Study[10]	AACES	USA	2011–16	0	0	0	0	595	743	0	0
Australian Ovarian Cancer and Australian Cancer Study[41]	AUS	Australia	2002–05	1268	1401	0	0	0	0	37	27
Connecticut Ovarian Cancer Study[42]	CON	USA	1999–2003	368	493	6	17	8	34	3	6
Diseases of the Ovary and their Evaluation Study[43,44]	DOV	USA	2002–09	1012	1679	33	40	11	29	55	47
Hawaii Ovarian Cancer Case-Control Study[45,46]	HAW	USA	1993–008	268	383	0	0	0	0	222	355
Hormones and Ovarian Cancer Prediction Study[47]	HOP	USA	2003–09	700	1752	2	6	24	29	4	1
North Carolina Ovarian Cancer Study[48,49]	NCO	USA	1999–2008	777	832	6	11	112	180	7	5
New England Case-Control Study of Ovarian Cancer[50,51]	NEC	USA	1992–2008	1427	2030	6	10	20	23	24	10
Ovarian Cancer in Alberta and British Columbia Study	OVA	Canada	2002–12	1087	2271	0	0	1	3	55	80
Genetic Epidemiology of Ovarian Cancer[52]	STA	USA	1997–2002	325	349	49	62	16	66	73	73
University of California, Irvine Ovarian Cancer Study[53]	UCI	USA	1995–2005	339	495	32	21	0	0	21	8
Los Angeles County Case-Control Studies of Ovarian Cancer[5,54,55]	USC	USA	1993–2010	1347	1934	299	366	124	126	161	153
Totals				8918	13619	433	533	911	1233	662	765

data on the number of live births was unavailable in CON so the number of full-term births was used as a proxy. As in previous OCAC manuscripts, we defined recent BMI as BMI one year before the reference date except for CON, DOV and HAW, where 5 years before the reference date was used.[11] Analgesic medication use was defined as medication use at least once per week.[12] Three sites had missing data on analgesic medications for specific ascertainment periods: HAW did not collect data on analgesic medications between 1993 and 1999, NCO did not collect data on aspirin use for the first 2 years of the study and USC only provided data on analgesic medications collected during 2000–05.

Statistical analysis

All analyses were performed using SAS 9.4 (Cary, NC). Using multivariable logistic regression, we estimated odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between each characteristic and EOC risk separately for each self-reported racial/ethnic group: Non-Hispanic White, White Hispanic (herein, referred to as Hispanic), Black and Asian/Pacific Islander. Models were adjusted for age, study site and well-established risk factors with complete data across all studies: parity, duration of oral contraceptive use and family history of ovarian/breast cancer. To estimate the association between breastfeeding and EOC risk, data were restricted to parous women, and

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for the association between hormone therapy use (overall and estrogen only) and EOC risk, data were restricted to postmenopausal women. Within the study population, we assessed racial/ethnic heterogeneity in each risk factor association using a likelihood ratio test that compared a model where the OR for the risk factor of interest varied by race/ethnicity (Non-Hispanic Whites as the referent group) versus a model where the OR for the risk factor of interest did not vary by race/ethnicity. We used the false discovery rate[13] to correct for multiple comparisons.

To assess between-study heterogeneity, we used the *metaanal* SAS macro.[14] Within each racial/ethnic group, study-specific ORs were combined into a pooled estimate for each risk factor association, which was weighted by the reciprocal of the combined study-specific variance plus the across-studies variance under a random effects model.[15,16] Due to sparse data for Hispanics, Blacks and Asian/Pacific Islanders in some studies, we could only reliably estimate study-specific associations and assess study heterogeneity for Non-Hispanic Whites.

Given the heterogeneity of ovarian cancer, we repeated the analyses restricted only to the most common histotype, high-grade serous ovarian cancer (HGSOC).[17,18] We defined HGSOC as any patient diagnosed with serous histology and tumour grade ≥ 2 ($n = 5049$). As the majority of serous EOC is high-grade, serous cases with missing grade were classified as HGSOC ($n = 1162$). We re-classified cases with endometrioid histology and grade ≥ 2 as HGSOC ($n = 979$) because the majority are actually HGSOC.[19,20] Also, undifferentiated/poorly differentiated EOC with unspecified histology and grade ≥ 2 was considered HGSOC ($n = 183$). Therefore, 7,373 HGSOC cases were analysed.

In an effort to summarize the impact of differences in the distribution of risk factors for EOC by race/ethnicity on EOC incidence, we used a method described in Risch *et al.*[21] to calculate the average OR among the controls within each racial/ethnic group. We assumed that the controls comprised a representative sample of subjects within each racial/ethnic group, and the average OR within each racial/ethnic group was estimated according to the race/ethnicity-specific covariates of a model of established risk factors for EOC (parity, oral contraceptive use, family history of ovarian or breast cancer, endometriosis and tubal ligation) with additional adjustment for age and study site (See Supplementary Methods, available as Supplementary data at *IJE* online). The average OR represents a mean OR across the control distribution of the modelled covariates of interest, with respect to a fully unexposed individual, and as adjusted for other covariates as needed. In this case, a fully unexposed individual is a woman that was ever pregnant, used oral contraceptives, does not have a family history of ovarian or breast cancer, does not have a history of endometriosis, and had a tubal ligation.

Because self-reported race/ethnicity and genetic ancestry may disagree somewhat,[22] we determined the concordance between self-identified race/ethnicity and genetically inferred ancestry among women who had available genetic data (5866 cases, 8754 controls). As described in Amos, *et al.*,[23] the FastPop R package[24] was used to estimate the proportion of intercontinental ancestry using 2318 ancestry informative markers with minor allele frequencies ≥ 0.05. The proportion of European, African and Asian ancestry was estimated for each individual, summing to 100%. Women with a proportion of >80% European ancestry were considered European and women with >50% African and >50% Asian ancestry were considered African and Asian, respectively. The concordance for Hispanics was not evaluated because the term 'Hispanic' is more indicative of ethnicity and Hispanics are typically an admixture of European, Native American and African ancestry.[25,26]

Results

We identified 10 924 women with invasive EOC and 16 150 controls with available data on race/ethnicity and adjusted covariates (age, study site, parity, duration of oral contraceptive use and family history of ovarian or breast cancer) (Table 1). The prevalence of most characteristics differed considerably by race/ethnicity (Table 2). Hispanic and Black women were more likely to have three or more births, whereas Asian/Pacific Islanders less frequently reported oral contraceptive use. A striking difference in BMI was observed; among controls, 51% of Black women were obese compared with 25% of Hispanics, 21% of Non-Hispanic Whites and only 5% of Asian/Pacific Islanders. Black women were more likely to report use of body powders and to have had a hysterectomy and a tubal ligation. Hispanic women reported lower levels of educational attainment, with 26% of Hispanic controls having less than a high school education. Breastfeeding was more common among Asian/Pacific Islanders and was least prevalent among Black women, and Non-Hispanic White women were more likely than other racial/ethnic groups to report use of hormone therapy. The most common histotype and tumour stage was HGSOC and distant stage, respectively. The distribution of histotype and stage was similar among racial/ethnic groups except for Asian/Pacific Islanders who were more frequently diagnosed with clear cell EOC and less frequently diagnosed with HGSOC and distant stage disease.

Estimated ORs and 95% CIs for the association between each characteristic and EOC risk are shown in Table 3,

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Table 2. Frequency distribution of participant characteristics by racial/ethnic group

Participant characteristics	Race/rthnicity							
	Non-Hispanic White		Hispanic		Black		Asian/Pacific Islander	
	Cases ($n = 8918$)	Controls ($n = 13619$)	Cases ($n = 433$)	Controls ($n = 533$)	Cases ($n = 911$)	Controls ($n = 1233$)	Cases ($n = 662$)	Controls ($n = 765$)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Age								
18–50 years	2242 (25)	4355 (32)	155 (36)	286 (54)	245 (27)	439 (36)	310 (47)	344 (45)
51–60 years	2923 (33)	4385 (32)	142 (33)	147 (27)	294 (32)	430 (35)	162 (25)	197 (26)
≥61 years	3753 (42)	4879 (36)	136 (31)	100 (19)	372 (41)	364 (29)	190 (29)	224 (30)
Parity								
0 live births	2230 (25)	2240 (16)	84 (19)	73 (14)	164 (18)	166 (13)	220 (33)	151 (20)
1 live birth	1250 (14)	1797 (13)	65 (15)	73 (14)	163 (18)	237 (19)	118 (18)	128 (17)
2 live births	2689 (30)	4802 (35)	93 (21)	139 (26)	209 (23)	339 (28)	167 (25)	246 (32)
≥3 live births	2749 (31)	4790 (35)	191 (44)	248 (46)	375 (41)	491 (40)	157 (24)	240 (31)
Duration of oral contraceptive use								
Never used	3521 (40)	3623 (27)	224 (52)	202 (38)	311 (34)	306 (25)	437 (66)	385 (50)
<5 years	3132 (35)	4819 (35)	139 (32)	198 (37)	363 (40)	526 (43)	165 (25)	232 (30)
≥5 years	2265 (25)	5177 (38)	70 (16)	133 (25)	237 (26)	401 (32)	60 (9)	148 (19)
Family history of ovarian/breast cancer[a]								
No	7065 (79)	11409 (84)	363 (84)	476 (89)	677 (74)	1041 (84)	589 (89)	680 (89)
Yes	1853 (21)	2210 (16)	70 (16)	57 (11)	234 (26)	192 (16)	73 (11)	85 (11)
Recent BMI[b]								
Normal (<25 kg/m^2)	3518 (48)	5458 (50)	140 (37)	201 (43)	161 (18)	238 (21)	382 (73)	445 (74)
Overweight (25–29.9 kg/m^2)	2117 (29)	3159 (29)	125 (33)	151 (32)	243 (27)	325 (28)	108 (20)	126 (21)
Obese (≥30 kg/m^2)	1739 (23)	2328 (21)	113 (30)	116 (25)	485 (55)	594 (51)	35 (7)	33 (5)
Missing	132	54	6	3	5	7	9	8
Hysterectomy[c]								
No	7176 (81)	11304 (83)	362 (84)	478 (90)	599 (66)	957 (78)	595 (90)	707 (93)
Yes	1705 (19)	2273 (17)	70 (16)	54 (10)	310 (34)	273 (22)	66 (10)	57 (7)
Missing	37	42	1	1	2	3	1	1
Tubal ligation[d]								
No	6983 (82)	9732 (75)	332 (83)	383 (75)	614 (68)	747 (61)	565 (88)	620 (82)
Yes	1536 (18)	3310 (25)	69 (17)	127 (25)	294 (32)	483 (39)	76 (12)	136 (18)
Missing	60	82	0	2	3	3	0	1
Age at menarche								
<12 years	1824 (21)	2779 (21)	104 (24)	143 (27)	223 (25)	329 (27)	124 (19)	163 (21)
12–13 years	4881 (55)	7477 (55)	220 (51)	245 (46)	457 (50)	593 (48)	315 (48)	365 (48)
≥14 years	2134 (24)	3265 (24)	108 (25)	144 (27)	230 (25)	311 (25)	214 (33)	234 (31)
Missing	79	98	1	1	1	0	9	3
History of endometriosis								
No	6675 (89)	10115 (92)	359 (94)	447 (95)	809 (91)	1113 (96)	461 (87)	566 (93)
Yes	790 (11)	845 (8)	21 (6)	22 (5)	81 (9)	49 (4)	67 (13)	44 (7)
Missing	41	39	4	2	4	2	6	2
Education								
Less than high school	839 (10)	790 (6)	115 (35)	103 (26)	129 (15)	147 (12)	70 (11)	67 (9)
≥High school graduate	7473 (90)	11884 (94)	210 (65)	290 (74)	734 (85)	1048 (88)	573 (89)	675 (91)
Missing	606	945	108	140	48	38	19	23
Body powder use								
Never use	3273 (53)	5447 (59)	220 (64)	311 (73)	354 (42)	537 (50)	313 (75)	366 (74)
Any genital use	1876 (30)	2227 (24)	60 (18)	65 (15)	344 (40)	335 (31)	36 (9)	38 (8)
Body/non-genital use	1029 (17)	1500 (16)	61 (18)	50 (12)	150 (18)	203 (19)	70 (17)	90 (18)
Missing	621	837	5	7	38	55	91	104
Breastfeeding[e]								
No	2831 (44)	3817 (35)	170 (52)	219 (50)	500 (67)	650 (61)	123 (29)	143 (24)
Yes	3601 (56)	7140 (65)	154 (48)	220 (50)	247 (33)	417 (39)	306 (71)	465 (76)

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Table 2. Continued

Participant characteristics	Race/rthnicity							
	Non-Hispanic White		Hispanic		Black		Asian/Pacific Islander	
	Cases ($n = 8918$)	Controls ($n = 13619$)	Cases ($n = 433$)	Controls ($n = 533$)	Cases ($n = 911$)	Controls ($n = 1233$)	Cases ($n = 662$)	Controls ($n = 765$)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Aspirin use[f]								
No	4173 (80)	6132 (79)	145 (82)	172 (88)	604 (85)	878 (85)	229 (87)	231 (81)
Yes	1051 (20)	1625 (21)	32 (18)	23 (12)	110 (15)	155 (15)	35 (13)	53 (19)
Missing	2282	3242	207	276	180	131	270	328
Acetaminophen use[f]								
No	4316 (80)	6358 (80)	155 (87)	169 (87)	621 (84)	909 (86)	234 (88)	245 (86)
Yes	1062 (20)	1554 (20)	23 (13)	25 (13)	116 (16)	148 (14)	32 (12)	39 (14)
Missing	2128	3087	206	277	157	107	268	328
NSAID use[f]								
No	3881 (73)	5655 (72)	125 (73)	148 (79)	546 (74)	777 (74)	221 (85)	246 (88)
Yes	1428 (27)	2164 (28)	47 (27)	39 (21)	191 (26)	280 (26)	39 (15)	34 (12)
Missing	2197	3180	212	284	157	107	274	332
Hormone therapy use[g]								
No	3163 (49)	4122 (47)	171 (61)	160 (61)	474 (73)	574 (74)	211 (58)	211 (54)
Yes	3266 (51)	4703 (53)	110 (39)	103 (39)	171 (27)	202 (26)	153 (42)	180 (46)
Missing	37	48	2	1	5	2	0	0
Any estrogen-only therapy use[g]								
No	2480 (65)	3523 (65)	158 (72)	143 (77)	468 (79)	554 (83)	187 (76)	186 (71)
Yes	1311 (35)	1865 (35)	61 (28)	43 (23)	121 (21)	114 (17)	59 (24)	76 (29)
Missing	1212	2109	37	43	49	63	71	97
Histology								
Serous								
High-grade serous[h]	6060 (68)		303 (70)		669 (76)		341 (52)	
Low-grade serous	288 (3)		23 (5)		27 (3)		4 (1)	
Mucinous	455 (5)		38 (9)		52 (6)		77 (12)	
Endometrioid (low-grade)	532 (6)		18 (4)		26 (3)		45 (7)	
Clear cell	609 (7)		17 (4)		28 (3)		120 (18)	
Mixed	296 (3)		3 (1)		11 (1)		13 (2)	
Other or unspecified epithelial	660 (7)		31 (7)		69 (8)		61 (9)	
Missing	164		0		29		1	
Stage								
Localized	1364 (18)		81 (19)		147 (18)		195 (33)	
Regional	1307 (17)		67 (16)		130 (15)		126 (21)	
Distant	5053 (65)		279 (65)		558 (67)		275 (46)	
Missing	107		6		75		11	

Number of participants with missing data was determined from only those sites that provided data for that covariate. The following variables were not available or considered missing for certain sites: body powder exposure (CON, OVA, STA, UCI); endometriosis (OVA, STA); analgesic medications (OVA, STA); BMI (OVA, STA); tubal ligation (UCI); breastfeeding (UCI); estrogen-only hormone therapy use (AUS, CON, STA); stage (OVA).

[a]Family history of ovarian/breast cancer in a first-degree relative.

[b]Recent BMI is defined as BMI 1 year before reference date (interview date for controls and diagnosis date for cases) for AAS, AUS, HOP, NCO, NEC, UCI and USC or 5 years before reference date for CON, DOV and HAW.

[c]Hysterectomy that occurred at least 1 year before the reference date.

[d]Tubal ligation that occurred at least 1 year before the reference date.

[e]Breastfeeding was assessed among women who had one or more live births.

[f]Analgesic medication use was defined as use at least once a week. Three sites had missing data on analgesic medications for specific ascertainment periods: HAW did not collect data on analgesic medications between 1993 and 1999, NCO did not collect data on aspirin use for the first 2 years of the study and USC only provided data on analgesic medications collected during 2000–05.

[g]Hormone therapy use was assessed among postmenopausal women.

[h]HGSOC was defined as any patient diagnosed with serous histology and tumour grade ≥2 or missing, endometrioid histology and grade ≥2, and undifferentiated/poorly differentiated EOC with unspecified histology and grade ≥2.

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Table 3. Estimated ORs and 95% CIs for the association between participant characteristics and invasive ovarian cancer overall and stratified by racial/ethnic group

	Race/Ethnicity					
	Non-Hispanic White ($n = 22537$)	Hispanic ($n = 966$)	Black ($n = 2144$)	Asian/Pacific Islander ($n = 1427$)		
Participant characteristics	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	Exact P[a]	FDR P[a]
Parity					0.04	0.16
0 live births	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)		
1 live birth	0.69 (0.63–0.76)	0.83 (0.51–1.34)	0.67 (0.49–0.90)	0.65 (0.46–0.91)		
2 live births	0.53 (0.49–0.58)	0.53 (0.34–0.83)	0.57 (0.43–0.76)	0.48 (0.36–0.65)		
≥3 live births	0.45 (0.41–0.49)	0.50 (0.33–0.74)	0.59 (0.45–0.78)	0.38 (0.28–0.54)		
Duration of oral contraceptive use					0.46	0.68
Never used	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)		
<5 years	0.77 (0.72–0.83)	0.77 (0.57–1.05)	0.78 (0.63–0.97)	0.64 (0.49–0.84)		
≥5 years	0.48 (0.45–0.52)	0.56 (0.38–0.81)	0.63 (0.49–0.79)	0.38 (0.26–0.53)		
Family history of ovarian/breast cancer[b]					0.009	0.07
No	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)		
Yes	1.35 (1.25–1.45)	1.63 (1.10–2.43)	1.77 (1.42–2.21)	1.08 (0.75–1.53)		
Recent BMI[c]					0.95	0.95
Normal (<25 kg/m^2)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)		
Overweight (25–29.9 kg/m^2)	1.02 (0.95–1.10)	1.05 (0.75–1.48)	1.10 (0.84–1.45)	1.08 (0.80–1.47)		
Obese (≥30 kg/m^2)	1.19 (1.10–1.28)	1.16 (0.81–1.66)	1.19 (0.93–1.52)	1.59 (0.94–2.68)		
Hysterectomy[d]					0.0005	0.008
No	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)		
Yes	1.13 (1.05–1.22)	1.41 (0.94–2.12)	1.64 (1.34–2.02)	1.42 (0.95–2.12)		
Tubal ligation[e]					0.84	0.90
No	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)		
Yes	0.80 (0.74–0.86)	0.73 (0.51–1.05)	0.81 (0.66–1.00)	0.90 (0.65–1.25)		
Age at menarche					0.68	0.80
<12 years	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)		
12–13 years	0.98 (0.91–1.05)	1.19 (0.86–1.65)	1.11 (0.89–1.38)	1.15 (0.86–1.55)		
≥14 years	0.95 (0.87–1.03)	0.98 (0.68–1.43)	1.02 (0.79–1.31)	1.13 (0.81–1.56)		
History of endometriosis					0.04	0.16
No	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)		
Yes	1.43 (1.29–1.59)	1.20 (0.62–2.32)	2.42 (1.65–3.55)	1.87 (1.22–2.87)		
Education					0.14	0.31
Less than high school	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)		
≥High school graduate	0.70 (0.62–0.78)	0.59 (0.41–0.85)	0.94 (0.71–1.24)	0.85 (0.57–1.26)		
Body powder use					0.12	0.31
Never use	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)		
Any genital use	1.30 (1.20–1.41)	1.41 (0.93–2.13)	1.62 (1.32–2.00)	1.02 (0.61–1.70)		
Only non–genital use	1.00 (0.91–1.11)	1.55 (1.00–2.39)	1.13 (0.87–1.46)	0.82 (0.56–1.19)		
Breastfeeding[f]					0.23	0.46
No	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)		
Yes	0.75 (0.70–0.80)	1.21 (0.88–1.68)	0.77 (0.63–0.95)	0.76 (0.57–1.03)		
Aspirin use[g]					0.32	0.56
No	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)		
Yes	0.93 (0.85–1.02)	1.23 (0.66–2.31)	0.91 (0.68–1.20)	0.88 (0.52–1.48)		
Acetaminophen use[g]					0.70	0.80
No	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)		
Yes	1.02 (0.93–1.12)	0.85 (0.44–1.65)	1.21 (0.92–1.59)	1.08 (0.63–1.86)		
NSAID use[g]					0.47	0.68
No	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)		
Yes	0.95 (0.87–1.03)	1.48 (0.85–2.57)	0.99 (0.79–1.24)	1.47 (0.85–2.54)		

(continued)

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Table 3. Continued

	Race/Ethnicity					
	Non-Hispanic White ($n = 22537$)	Hispanic ($n = 966$)	Black ($n = 2144$)	Asian/Pacific Islander ($n = 1427$)		
Participant characteristics	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	Exact P[a]	FDR P[a]
Hormone therapy use[h]					0.58	0.77
No	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)		
Yes	0.95 (0.88–1.01)	1.06 (0.73–1.55)	1.07 (0.83–1.38)	0.94 (0.69–1.28)		
Any estrogen-only therapy use[h]					0.09	0.28
No	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)	1.00 (Referent)		
Yes	1.03 (0.94–1.13)	1.23 (0.76–1.98)	1.17 (0.87–1.58)	0.87 (0.56–1.33)		

All models adjusted for age (age at diagnosis for cases or age at interview for controls), study site, parity, duration of oral contraceptive use and family history of ovarian or breast cancer in a first-degree relative.

[a]Interaction was assessed by including cross-product interaction terms for each risk factor and race/ethnicity (Non-Hispanic White was the referent group) in a model of all racial/ethnic groups.

[b]Family history of ovarian/breast cancer in a first-degree relative.

[c]Recent BMI is defined as BMI 1 year before reference date (interview date for controls and diagnosis date for cases) for AAS, AUS, HOP, NCO, NEC, UCI and USC or 5 years before reference date for CON, DOV and HAW.

[d]Hysterectomy that occurred at least 1 year before the reference date.

[e]Tubal ligation that occurred at least 1 year before the reference date.

[f]Breastfeeding was assessed among women who had one or more live births.

[g]Analgesic medication use was defined as use at least once a week. Three sites had missing data on analgesic medications for specific ascertainment periods: HAW did not collect data on analgesic medications between 1993 and 1999, NCO did not collect data on aspirin use for the first 2 years of the study and USC only provided data on analgesic medications collected during 2000–05.

[h]Hormone therapy use was assessed among postmenopausal women.

stratified by racial/ethnic group. Risk factor associations were similar across race/ethnicity for most exposures. However, we observed statistically significant heterogeneity by race/ethnicity in the OR for hysterectomy [false discovery rate (FDR) corrected $P = 0.008$], where the association was strongest among Black women (OR = 1.64, 95% CI = 1.34–2.02) and appreciably different from that among Non-Hispanic White women (OR = 1.13, 95% CI = 1.05–1.22). Although not statistically significant after FDR correction, associations for parity, family history of ovarian or breast cancer, and endometriosis also varied by race/ethnicity. An inverse association with parity was observed for each racial/ethnic group, but the magnitude of the association was strongest among Asian/Pacific Islanders (≥3 live births: OR = 0.38, 95% CI = 0.28–0.54). The association with family history of ovarian or breast cancer was more pronounced among Black and Hispanic women (OR = 1.77, 95% CI = 1.42–2.21 and OR = 1.63, 95% CI = 1.10–2.43, respectively) compared with Non-Hispanic White women (OR = 1.35, 95% CI = 1.25–1.45), whereas no association was observed in Asian/Pacific Islanders. History of endometriosis was positively associated with EOC risk in all racial/ethnic groups, with the largest OR observed in Black women (OR = 2.42, 95% CI = 1.65–3.55).

Supplementary Table 1 (available as Supplementary data at *IJE* online) provides the estimated ORs and 95% CIs for the fixed and random effects models among Non-Hispanic Whites. Study heterogeneity was present for several characteristics (Q statistic P-value < 0.05 for duration of oral contraceptive use, recent BMI, hysterectomy, age at menarche, education, body powder exposure and NSAID use); however, the risk factor associations were similar for the fixed and random effects models and the conclusions remained the same.

The results of the analyses restricted to women diagnosed with HGSOC are shown in Supplementary Table 2 (available as Supplementary data at *IJE* online). In comparison with the overall results, the associations in HGSOC were weaker in magnitude for parity and endometriosis, yet stronger in magnitude for family history of ovarian or breast cancer and for body powder exposure. The magnitude and direction of the associations for all other examined risk factors were similar for EOC overall and HGSOC. Yet, racial/ethnic heterogeneity was not observed for any characteristic after correction for multiple comparisons.

For a model of established EOC risk factors (parity, oral contraceptive use, family history of ovarian or breast cancer, tubal ligation and endometriosis), the average ORs among the controls were estimated by race/ethnicity. Non-Hispanic Whites and Hispanics had the largest average ORs (OR = 1.90, 95% CI = 1.70–2.10 and OR = 1.90, 95% CI = 1.21–2.59, respectively) followed by Asian/Pacific Islanders (OR = 1.41, 95% CI = 0.84–1.97) and Blacks (OR = 1.18, 95% CI = 0.83–1.53) (data not shown).

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Genetically inferred ancestry and self-reported race/ethnicity were in high concordance; 99.2% of the women who self-identified as Non-Hispanic White were of European ancestry, 96.2% of the women who identified as Black were of African ancestry and 93.2% of the women who identified as Asian/Pacific Islander were of Asian ancestry (data not shown). Defining race/ethnicity by genetic ancestry rather than self-reports had minimal to no effect on our results.

Discussion

Our pooled analysis provides the largest investigation, to date, of EOC risk factors by race/ethnicity. We evaluated 17 epidemiological risk factors, many of which have never been examined in specific racial/ethnic groups, particularly Hispanics and Asian/Pacific Islanders (e.g. analgesic medication use, education, hysterectomy). We observed appreciable differences in the prevalence of several characteristics by race/ethnicity, most notably for parity, recent BMI and education. Most of the associations were similar across race/ethnicity, but the strength of the association with hysterectomy differed by race/ethnicity although all ORs were in the same direction.

In general, our findings comparing risk factor associations by race/ethnicity are consistent with the limited number of published studies in this area.[5–8] Two of these reports, Wu *et al.*[5] and Moorman *et al.*[6] provide results from OCAC studies included in the present manuscript, USC and NCO respectively, and are not independent from the current study. The only notable difference between Blacks and Whites was reported by Ness *et al.*[7] for the association between breastfeeding duration and EOC risk; however, this study was small, including only 84 Black women with ovarian cancer.

We observed racial/ethnic heterogeneity for the association between hysterectomy and EOC risk, with a more pronounced association among Black women in comparison with other racial/ethnic groups. It is possible that the prevalence of benign gynaecological conditions that are indications for hysterectomy may confound this association. The incidence of uterine fibroids, a common indication for hysterectomy, is higher among Black women in comparison with Whites and contributes to a higher rate of hysterectomy in this population.[27,28] However, the association between hysterectomy and risk of EOC was not in the expected direction. Epidemiological studies before 2000 suggest that women who have undergone a hysterectomy have a lower risk of EOC;[29] however, along with several recent studies,[6,30–32] we observed a positive association between hysterectomy and EOC risk. A meta-analysis by Jordan *et al.*[33] speculates that a temporal shift may have occurred in this association, possibly related to changes in hormone therapy recommendations and patterns of hormone therapy use over time. Peres *et al.*[34] evaluated this hypothesis in AACES, which was included in the present analysis, and observed an inverse association for premenopausal hysterectomy and EOC risk only among women using estrogen therapy. However, Peres *et al.*[34] also observed an inverse association for premenopausal hysterectomy after adjustment for indications of surgery (e.g. uterine fibroids, ovarian cysts) irrespective of hormone therapy use. A further investigation of this association, with more attention to secular trends, indication of surgery and hormone therapy use, is warranted.

Some of the racial/ethnic differences in risk factor associations may be due to racial/ethnic differences in the prevalence of histotypes, which have unique risk factor patterns.[35] For example, Asian/Pacific Islanders are more commonly diagnosed with clear cell EOC,[36] and although reproductive risk factors are associated with EOC overall, they are more strongly associated with clear cell EOC compared with the other histotypes.[35,37,38] In this study, Asian/Pacific Islanders had a higher prevalence of clear cell EOC and had a stronger association with parity in comparison with other racial/ethnic groups. However, our ability to examine race/ethnicity specific differences in the less common histotypes was hindered by insufficient power.

In the exploratory analysis of the average ORs among the controls by race/ethnicity, the CIs for the average ORs of Blacks and Non-Hispanic Whites did not overlap, indicating that there was appreciable heterogeneity between these two racial/ethnic groups. These results suggest that the distribution of established risk factors account for more of the incidence of EOC in Non-Hispanic Whites than Blacks. The average ORs also track reasonably well with EOC incidence rates by race/ethnicity, where the highest average OR and highest EOC incidence rate are in Non-Hispanic Whites.[2] This analysis is dependent on the assumption that the controls from each study are representative of the underlying population within each racial/ethnic group, which may be appropriate since the controls in each of these studies were population-based controls.

Although consortial data increase the potential to examine EOC risk factor associations by race/ethnicity, such data present several challenges. This analysis included only case-control studies where the exposure information was based on self-report. A concern with self-reported data is recall bias, especially for characteristics that are difficult to report with accuracy, require subjective summarization or can be influenced by the investigator, media or similar factors. Such problematic characteristics may include body powder exposure, analgesic medication use, breastfeeding and possibly family history. Additionally, several studies

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did not collect information on certain covariates and data were missing at the respondent-level for some women. Missing data limited our ability to evaluate certain characteristics in further detail, such as analgesic medication use where dose and duration may impact on the association with EOC risk.[12,39] Nevertheless, even with missing data, we had improved power over previously published race-specific analyses, because of the large sample size afforded by pooling AACES and OCAC studies. Some of the race-specific analyses in the non-White racial/ethnic groups were still limited by sample size, especially with respect to evaluating study heterogeneity. Another limitation stems from the OCAC data grouping all Hispanic and all Asian/Pacific Islander women into single categories, although cultural and genetic diversity exists within these groups.[26,40] Such grouping may have masked potential differences in risk factor prevalence and the corresponding associations across Hispanic and Asian/Pacific Islander subgroups.

By combining AACES and OCAC studies, the current analysis provides one of the largest and most comprehensive assessments of a variety of epidemiological characteristics in EOC by race/ethnicity. Although we observed racial heterogeneity for hysterectomy, our findings support the validity of EOC risk factors across all racial/ethnic groups, and further suggest that any racial/ethnic population with a higher prevalence of a modifiable risk factor should be targeted to disseminate information about prevention. A better understanding of the contributing causes to racial/ethnic differences in EOC incidence will be achieved with the inclusion of a greater proportion of non-White races/ethnicities in future epidemiological studies of EOC and by assessing additional risk factors beyond those included in this study, such as genetic susceptibility loci, area-level measures, migration and acculturation.

Supplementary Data

Supplementary data are available at *IJE* online.

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